REMARKS

Reconsideration and withdrawal of the objections to the specification and rejections of the claims, in view of the amendment and remarks herein, is respectfully requested. Claims 1-2, 7, 13, 15-16, 20, and 23 are amended; as a result, claims 1-2 and 4-53 are now pending in this application. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims present prior to amendment, which claims are in a continuing application of the above-referenced pending application.

Claims 13, 15-16, 20, and 23 were objected to under 37 C.F.R. § 1.75(c) as being in improper form. Claims 13, 15-16, 20, and 23 are amended to address the objection under 37 C.F.R. § 1.75(c).

The specification is amended at pages 43 and 75.

The Objections to the Specification

The specification was objected to because 1) doxorubicin, doxyrubicin and DOXIL® are all are referred to as "DOX" in the specification but are not identical and so should be clearly and explicitly identified throughout the disclosure; 2) Miglyol is a registered trademark name but that term is not identified accordingly in the specification; 3) the unit DF* is not defined; and 4) the specification does not adequately identify the "DOX" compound whose effects are graphed in Figures 5-10.

The amendments to the specification address items 2) and 3) above.

With regard to "doxorubicin" and "doxyrubicin", Applicant noted in the Amendment filed on August 21, 2007 that those terms are synonymous. Moreover, one of ordinary skill in the art would recognize that those terms are synonymous (e.g., see the abstracts for Djaldetti et al., Basic Res. Cardiol., 83:672 (1988) and Gross et al., Arzheimittelforschung, 26:130 (1976)) (a copy of each is enclosed herewith).

Although that specification discloses that the bioavailability of DOXIL® to cell culture cells is unclear, as the active ingredient in DOXIL® is doxorubicin, in the context of the

particular data disclosed in the specification (*in vitro* versus *in vivo*), one of skill in the art would understand the meaning of "DOX." That is, as DOXIL® is likely not bioavailable to culture cells, any response to "DOX" in cells *in vitro* would necessarily not be a response DOXIL®, e.g., the "DOX" employed to generate the data in Figures 5 and 7-10 was clearly not DOXIL®, as the data was obtained using airway epithelial cells, i.e., the data was obtained from cells *in vitro*. The data in Figure 6 was obtained after intranasal administration of rAAV and Z-LLL and doxorubicin (see page 78). Note that *in vivo* DOXIL® administration is mentioned in the Examples on pages 73-76 (referring to Figures 1 and 3) , then on pages 100-101 (where doxorubicin and DOXIL® are each referred to). Moreover, regardless of the "DOX" formulation, the active agent in those formulations is doxorubicin.

Thus, withdrawal of the objections to the specification is respectfully requested.

The 35 U.S.C. § 112, Second Paragraph, Rejections

Claims 1-2, 4-7, 13, 15-16, 20, and 23 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for 1) not reciting the preamble in the body of claims 1 and 2, and 2) reciting a trademark in claim 20. The amendments to claims 1-2 and 20 render the § 112(2) rejections moot.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-2, 4-7, 13, 15-16, 20, and 23 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Claims 1-2, 4-7, 13, 15-16, 20, and 23 were also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

The Examiner asserts that the issue for the purpose of written description is the lack of description of agents possessing the required functional properties and mammalian cells with aberrant ENaC expression or activity. The Examiner continues asserting that the specification does not disclose any identifying characteristic as to how an artisan would have identified and differentiated one structurally and functionally distinct compound that possesses any one of the

properties from another compound that might possess those properties, and that the breadth of aberrant expression or activity of ENaC genes is not fully described in the art because the art has not identified quantitative measurements objectively determine what is "aberrant".

To provide an adequate written description for a claimed genus, the specification can provide a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)).

The claims are directed to methods of screening for agents with a specific second activity. It is Applicant's position that agents that enhance viral transduction and methods to identify those agents are well known to the art (see, for example, Duan et al., J. Clin. Invest., 105:1573 (2000), a reference cited against the claims under § 103, and Examples 1-2, 4-5 and 7 in the specification). Moreover, methods to detect agents that inhibit expression or activity of ENaC are disclosed in the specification (see Examples 8-9), and agents for screening in the recited methods are disclosed at pages 4-6 and 27-34, and Examples 1-2 and 4 in the specification (i.e., more than one species is disclosed).

With regard to mammalian cells with increased ENaC expression or activity (claim 2), the Examiner is requested to note that the claims do not recite that the ENaC activity or expression in the mammalian cells is quantitatively determined. Nevertheless, as amended, claim 2 recites that the cells employed to screen compounds are those which have increased transcription of one or more of the ENaC subunits relative to corresponding cells with a wild-type CFTR gene.

As the recited agents and mammalian cells have a relevant identifying characteristic, the specification and claims are in compliance with the written description requirement of § 112(1).

With regard to enablement, the Examiner asserts that the specification fails to disclose the quantitative values and relationships linking the claimed limitations. Specifically, the Examiner asserts that i) there is no definition by which the expression or activity of the genus of claimed

sodium channels is to be considered "aberrant"; ii) there is no guidance or direction to the artisan as to the degree by which a disease is associated with changes in expression or activity of an epithelial sodium channel; and iii) the specification fails to disclose the necessary guidance to the artisan for choosing *a priori* an agent that inhibits expression or activity of ENaC having α, β and γ subunits of ENaC, other than doxorubicin.

35 U.S.C. § 112, first paragraph, requires that the specification provides an enabling disclosure for the claimed invention. The claims are directed to methods of screening for agents with a specific second activity. As discussed above, agents that enhance viral transduction and methods to identify those agents are well known to the art, and the specification discloses . methods to detect agents that inhibit expression or activity of ENaC, and agents for screening in the recited methods. The pending claims do not recite "aberrant" (basis i above) or "disease" (basis ii above).

With regard to basis iii) for the rejection, the Examiner is requested to consider that it is well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Thus, if Applicant's invention is disclosed so that one of ordinary skill in the art can practice the claimed invention, even if the practice of the invention by the art worker includes routine screening or some experimentation, Applicant has complied with the requirements of 35 U.S.C. § 112, first paragraph. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976); Ex parte Jackson, 217 U.S.P.Q. 804 (Bd. App. 1982).

The fact that the outcome of the claimed screening program may be unpredictable is precisely why a screening program is carried out. It simply cannot reasonably be contended that

a program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

The Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate biomolecules with particular properties do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to screen agents to identify those with the recited dual activities. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a variety of agents is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Ex parte Forman, 230 U.S.P.Q.2d 456 (Bd. App. 1986).

Therefore, the specification, in view of the knowledge in the art, clearly satisfies the enablement requirement of § 112(1).

Thus, withdrawal of the § 112(1) rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 1, 4-5, 13, 15-16, 20, and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwarzbach et al. (Int. J. Oncology, 20:1211 (2002)) in view of Duan et al. (J. Clin. Invest., 105:1573 (2000)) and Bruno et al. (FEBS Letters, 427:241 (1998)), as evidenced by Kiyomiya et al. (Int. J. Oncol., 20:1205 (2002)). Claims 2, 4, 6-7, 13, 15-16, 20, and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwarzbach et al. in view of Duan et al., Bruno et al., and Johnson et al. (Nature Genetics, 2:21 (1992)), as evidenced by Kiyomiya et al. These rejections are respectfully traversed.

Schwarzbach et al. disclose that the cytotoxic effect of doxorubicin treatment (for 12-24 hours) on human sarcoma cell lines was enhanced by subsequent infection with AAV-2 (abstract and page 1212). Not all of the tested cell lines, however, exhibited this effect (see Figure 1), and the effective amount of doxorubicin varied (Figure 4). There is no mention in Schwarzbach et al. of the effect doxorubicin had on AAV transduction.

Duan et al. disclose that LLL or Z-LLL enhances AAV transduction in epithelial cells *in vitro* and *in vivo* and in liver *in vivo*.

Bruno et al. relate that expression of a core subassembly subunit of human RNA polymerase in a doxorubicin resistant cancer cell line increased the sensitivity of the cells to doxorubicin.

Kiyomiya et al. disclose a mechanism for the nuclear localization of adriamycin, which localization involves proteosomes.

Johnson et al. disclose that a gene transfer efficiency of 100% with a CFTR gene is not necessary to restore normal airway epithelial function in cystic fibrosis airway cells. That conclusion was based on mixing populations of cystic fibrosis airway cells, one of which expressed a wild-type CFTR gene and the other of which expressed a reporter gene.

None of Schwarzbach et al., Duan et al., Bruno et al., Kiyomiya et al., or Johnson et al. relate to a screening assay for agents with the recited dual properties, or disclose or suggest contacting mammalian cells having increased expression or activity of ENaC with an agent that enhances transduction viral gene therapy vector or identifying one or more agents which inhibit expression or activity of ENaC that also enhance viral gene transduction. In fact, none of the cited documents refers to ENaC.

Thus, it is unclear how it would be purportedly obvious to one of skill in the art to identify agents that alter ENaC expression or activity and alter viral transduction, in view of art that discloses that doxorubicin is a chemotherapeutic (i.e., doxorubicin kills cells) and may be transported to the nucleus of cells via proteosomes, that overexpression of a subunit of RNA polymerase may at least partially overcome doxorubicin resistance of cancer cells, and that LLL and Z-LLL enhance AAV transduction.

It is only Applicant's specification that discloses a screening assay to identify agents that enhance viral, e.g., AAV, transduction and inhibit increased expression or activity of ENaC, and so may be useful in disorders such as CF.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date May 14, 2008

By
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 14th day of May 2008.

CANDIS BUENDING

Name

Signature

1: Arzneimittelforschung. 1976;26(1A):130-5.

[Clinical problems of optimum bioavailability, in particular in cytostatic therapy (author's transl)]

[Article in German]

Gross R, **Hirschmann WD**.

The clinical application of cytostatic drugs requires knowledge of their biochemistry, pharmacology, pharmacokinetics as well as their action at the cellular level within the generation cycle. The principles apply to tumor cells as well as to normal, rapidly proliferating tissues. The intensive research on cancer treatment all over the world is leadin to a rapid accumulation of experimental data about the action of single cytostatic drugs in tissue culture and on transplantable animal tumor systems, especially in rodents. Clinical chemotherapy in human malignancies today preferentially uses combinations of different cytostatics. Inumerable combinations of drugs are available, especially if variations in respect to drug dose and intervals of drug application are taken into consideration. The experimental basis for such combinations of drugs and drug interactions is scanty. Using th pyrimidine analog cytosine arabinoside and the two antibiotics daunorubicin and doxyrubicin (adriamycin) as examples, it is demonstrated that information on the pharmacolinetic behaviour of cytostatic drugs is a prerequisite for their success in clinical application, but is on its own insufficient to predict the tumor response.

Publication Types:
- English Abstract

PMID: 947192 [PubMed - indexed for MEDLINE]

1: Basic Res Cardiol. 1988 Nov-Dec;83(6):672-7.

SEM observations on the effect of anthracycline drugs on cultured newborn rat cardiomyocytes.

Djaldetti M, Gilgal R, Shainberg A, Klein B, Zahavi I.

Department of Medicine B, Hasharon Hospital, Petah-Tiqva, Israel.

The effect of two anthracyclines-doxorubicin hydrochloride (adriamycin) and 4'-epidoxorubicin (epirubicin) and an anthracenedione (novantrone) on the contractibility and surface ultrastructure of newborn rat cardiomyocytes cultured for five days was examined. While the beating rate of the cells was affected only by the anthracyclines, an alteration of the sarcolemma, disruption of the slender processes and swelling of the nuclei and/or the cells was observed following incubation with each of the three drugs for two hours. However, the damage induced by adriamycin was more pronounced than that induced by the other two drugs, when doses extrapolated from those accepted as therapeutic were compared.

PMID: 3223881 [PubMed - indexed for MEDLINE]